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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/04, A61K 31/44 — A1

(11) International Publication Number: WO 95/03297

(43) International Publication Date: 2 February 1995 (02.02.95)

(21) International Application Number: PCT/US94/08297

(22) International Filing Date: 21 July 1994 (21.07.94)

(30) Priority Data:
08/095,234 21 July 1993 (21.07.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/095,234 (CIP)
Filed on 21 July 1993 (21.07.93)

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(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMIDAZOLES FOR TREATING CYTOKINE MEDIATED DISEASE

(57) Abstract

Novel 2,4,5-triaryl imidazole compounds and compositions for use in therapy, such as cytokine mediated diseases.

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Imidazoles for Treating Cytokine Mediated Disease

This invention relates to a novel group of imidazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION:

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic ß cells.

Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

Interleukin -8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and ketainocytes. Its production from endothelidl cells is induced by IL-1, TNF, or lipopolysachharide (LPS). Human IL-8 has been shown to act on Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutophils, T-lymphocutes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutophils into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

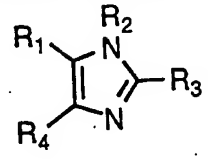
This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

Compounds of Formula (I) are represented by the structure:



(I)

wherein:

R_1 is 4-pyridyl, pyrimidinyl, quinazolin-4-yl, quinolyl, isoquinolinyl, 1-imidazolyl or 1-benzimidazolyl which is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} alkylthio, $NR_{10}R_{20}$, or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_2 is hydrogen, $-(CR_{10}R_{20})_n OR_{12}$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_{n'}OR_{13}$, $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}NR_8R_9$, $(CR_{10}R_{20})_{n'}NO_2$, $(CR_{10}R_{20})_{n'}CN$, $(CR_{10}R_{20})_{n'}SO_2R_{25}$, $(CR_{10}R_{20})_{n'}S(O)_mNR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)NR_{13}OR_{12}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}N(OR_{21})C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}N(OR_{21})C(Z)R_{13}$, $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$, $(CR_{10}R_{20})_{n'}NR_{10}C(=NR_{27})NR_8R_9$, $(CR_{10}R_{20})_{n'}OC(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)NR_8R_9$, $(CR_{10}R_{20})_{n'}NR_{10}C(Z)OR_{10}$, 5-($R_{25}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;wherein the aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl moieties may be optionally substituted;

n' is an integer having a value of 1 to 10;

m is 0, or the integer 1 or 2;

R_3 is or Q-(Y_1)t ;

Q is an aryl or heteroaryl group;

t is a number having a value of 1, 2 or 3;

Z is oxygen or sulfur;

n is 0 or an integer from 1 to 10;

Y_1 is independently selected from hydrogen, C_{1-5} alkyl, halo-substituted C_{1-5} alkyl, halogen, or $-(CR_{10}R_{20})_nY_2$;

Y_2 is $-OR_8$, $-NO_2$, $-S(O)_{m'}R_{11}$, $-SR_8$, $-S(O)_{m'}OR_8$, $-S(O)_mNR_8R_9$, $-NR_8R_9$, $-O(CR_{10}R_{20})_nNR_8R_9$, $-C(O)R_8$, $-CO_2R_8$, $-CO_2(CR_{10}R_{20})_{n'}CONR_8R_9$, $-ZC(O)R_8$, $-CN$, $-C(Z)NR_8R_9$, $-NR_{10}C(Z)R_8$, $-C(Z)NR_8OR_9$, $-NR_{10}C(Z)NR_8R_9$, $-NR_{10}S(O)_mR_{11}$, $-N(OR_{21})C(Z)NR_8R_9$, $-N(OR_{21})C(Z)R_8$, $-C(=NOR_{21})R_8$, $-NR_{10}C(=NR_{15})SR_{11}$, $-NR_{10}C(=NR_{15})NR_8R_9$, $-NR_{10}C(=CR_{14}R_{24})SR_{11}$, $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$, $-NR_{10}C(O)C(O)NR_8R_9$, $-NR_{10}C(O)C(O)OR_{10}$, $-C(=NR_{13})NR_8R_9$, $-C(=NOR_{13})NR_8R_9$, $-C(=NR_{13})ZR_{11}$, $-OC(Z)NR_8R_9$, $-NR_{10}S(O)_mCF_3$, $-NR_{10}C(Z)OR_{10}$, 5-(R_{18})-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

m' is a number having a value of 1 or 2;

R_4 is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substitiuent, is halo, cyano, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{23}$, $-(CR_{10}R_{20})_{m''}COR_{36}$, SR_5, $-SOR_5$, $-OR_{36}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{36}$, $-NR_{10}C(Z)R_{23}$, or $-(CR_{10}R_{20})_{m''}NR_{10}R_{20}$ and which, for other positions of substitution, is halo, cyano, $-C(Z)NR_{16}R_{26}$, $-C(Z)OR_8$, $-(CR_{10}R_{20})_{m''}COR_8$, $-S(O)_mR_8$, $-OR_8$, halo-substituted-C_{1-4} alkyl, $-C_{1-4}$ alkyl, $-(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_8$, $-NR_{10}S(O)_{m'}R_{11}$, $-NR_{10}S(O)_{m'}NR_7R_{17}$ $-ZC(Z)R_8$ or $-(CR_{10}R_{20})_{m'}NR_{16}R_{26}$; wherein m'' is 0 to 5 and m''' is 0 or 1;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR_7R_{17}$ and $-SOR_5$ being $-SOH$;

R_6 is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-5} cycloalkyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_8 is hydrogen, heterocyclyl, heterocyclylalkyl or R_{11};

R_9 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R_8 and R_9 may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R_{12} is hydrogen, -C(Z)R_{13} or optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted arylC_{1-4} alkyl, or S(O)$_2R_{25}$;

R_{13} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclylC_{1-10} alkyl , aryl, arylC_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl;

R_{14} and R_{24} is each independently selected from hydrogen, alkyl, nitro or cyano;

R_{15} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

R_{16} and R_{26} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12} ;

R_{18} and R_{19} is each independently selected from hydrogen, C_{1-4} alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;

R_{21} is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl ;

R_{22} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{23} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-5} cycloalkyl;

R_{36} is hydrogen or R_{23};

R_{25} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

R_{27} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl, or aryl;

or a pharmaceutically acceptable salt thereof;

and excluding 2-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-(4-pyridyl)imidazole, and 2-phenyl-4-phenyl-5-(4-pyridyl)imidazole.

FULL DESCRIPTION OF THE INVENTION

The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine inhibition or production. In particular, cytokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retovirus infections, such as but not limited to feline immunodeficiency virus (FIV),

bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

In Formula (I), preferred R_1 moieties are 4-pyrimidinyl, 4-pyridyl or 4-quinolyl groups of which the 4-pyrimidinyl and the 4-pyridyl are preferred. These groups are preferably substituted with a C_{1-4} alkyl, in particular methyl, or a $NR_{10}R_{20}$ group, preferably where R_{10} and R_{20} are both hydrogen. More preferred is the 4-pyridyl derivative substituted at the 2-position with a C_{1-4} alkyl, especially 2-methyl-4-pyridyl, or the 4-pyrimidinyl derivative substituted at the 2-position with C_{1-4} alkyl or $NR_{10}R_{20}$, more preferably with $NR_{10}R_{20}$, and R_{10} and R_{20} are preferably hydrogen.

In Formula (I), R_2 is preferably an optionally substituted C_{1-10} alkyl, an optionally substituted aryl, an optionally substituted heterocyclic alkyl or an optionally substituted heterocyclic ring. The alkyl chain while being of 1 to 10 carbons in length is preferably from 2 to 4 carbons, more preferably 3 in length. The alkyl chain is preferably substituted by an aryl, heteroaryl or heterocyclic moiety, or the alkyl chain is interrupted by an oxygen [$(CR_{10}R_{20})_{n'}OR_{13}$] or sulfur group[$(CR_{10}R_{20})_{n'}S(O)_mR_{25}$] (which may be optionally oxidized) or by an optionally substituted amine derivative [$(CR_{10}R_{20})_{n'}NR_8R_9$]. Other substituted alkyl groups include $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$, or $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$. R_2 is may also be hydrogen when R_4 is not an unsubstituted pyridyl and R_3 a substitututed phenyl.

Preferred optionally substituted alkyl groups include, methyl $S(O)_mC_{1-4}$ alkyl- (wherein m is 0, 1 or 2), a methylsulfonamido alkyl-, an aryloxyalkyl-, such as phenoxyalkyl-, or an alkoxyalkyl-, such as ethoxy alkyl, optionally substituted (mono- or di-) amine derivatives include, aminoalkyl-, diethylaminoalkyl, (phenylmethyl-N-methyl)aminoalkyl, (phenylmethyl)amino-1-propyl, or the amino substituents may cyclize to form a 5 to 7 membered heteroring and optionally contain an additional heteroatom, such as a morpholino, pyrrolidinyl, or a piperidinyl group, such as piperidinyl alkyl, pyrrolidinylalkyl, morpholinoalkyl, wherein the alkyl is preferably 1 to 10 carbons in length is preferably from 2 to 4 carbons, more preferably 3 in length. It is recognized that if the amine derivatives cyclize the terms may overlap that of the heterocyclic alkyl derivatives.

More preferably R_2 is an optionally substituted C_{1-10} alkyl, an optionally substituted heterocyclyl ring, an optionally substituted heterocyclylC_{1-10} alkyl, an optionally substituted aryl, $(CR_{10}R_{20})_{n'}NR_8R_9$, or $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$ group.

When R_2 is an optionally substituted heterocyclyl C_{1-10} alkyl group, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. Preferably this alkyl

moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred heterocyclic alkyl groups include but are not limited to, morpholino ethyl, morpholino propyl, pyrrollidinyl propyl, and piperidinyl propyl moieties. The heterocyclyl ring may be optionally substituted one to four times independently by halogen; C_{1-4} alkyl; aryl, such as phenyl; aryl alkyl, such as benzyl- wherein the aryl or aryl alkyl moieties themselves may be optionally substituted (as in the definition section below); $C(O)OR_{13}$, such as the $C(O)C_{1-4}$ alkyl or C(O)OH moieties; C(O)H; $C(O)C_{1-4}$ alkyl, hydroxy substituted C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl (wherein m is 0, 1, or 2), $NR_{10}R_{20}$ (wherein R_{10} and R_{20} are independently hydrogen or C_{1-4}alkyl).

When R_2 is an optionally substituted heterocyclyl the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. When the ring is optionally substituted the substituents may be directly attached to the free nitrogen, such as in the piperidinyl group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. The heterocyclyl ring may be optionally substituted one to four times independently by the same substituents noted above for the heterocyclic alkyl groups.

Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i.e. a 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2 or 6 position or both, such as 2,2,6,6-tetramethyl-4-piperidine. Simiarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are aldo directly on the available nitrogen. The substitution on the heterocyclic ring is preferably the same regardless if it is a heterocyclic or heterocylic alkyl moiety.

When R_2 is an optionally substituted C_{3-7}cycloalkyl, or an optionally substituted C_{3-7}cycloalkyl C_{1-10} alkyl, the cycloalkyl group is preferably a C_5 to C_6 ring which ring may be optionally substituted one or more times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_m$ alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; or where the R_7R_{17} may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF_3; hydroxy substituted C_{1-10}alkyl; $C(O)OR_{13}$, such as the free acid or methyl ester derivative; an optionally

substituted aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl of phenethyl; and further where these aryl moieties may also be substituted one to two times by halogen; hydroxy; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; alkyl or halosubstituted alkyl.

When R_2 is $(CR_{10}R_{20})_{n'}NR_8R_9$, R_8 and R_9 are as defined in Formula (I), preferably R_8 and R_9 are each independently selected from hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl or an optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12}. It is recognized that in some instances this can yield the same moiety as a heterocyclic C_{1-10} alkyl moiety noted above which is also a suitable R_2 variable. Preferably R_8 and R_9 are independently hydrogen, C_{1-4} alkyl, preferably methyl, or benzyl. The n term is preferably 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred groups include, but are not limited to, aminopropyl, (N-methyl-N-benzyl)aminopropyl, (N-Phenylmethyl)amino-1-propyl, or diethylamino propyl.

When R_2 is a $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$ group, R_{13} is suitably hydrogen, C_{1-4} alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group. Preferred groups include, but are not limited to, carboxymethyl-1-butyl, carboxy-1-propyl, or 2-acetoxyethyl.

When R_2 is a $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$ group m is 0, 1, or 2, and R_{18} is preferably aryl, especially phenyl, or C_{1-10} alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a $(CR_{10}R_{20})_{n'}OR_{13}$ group, R_{13} is suitably hydrogen, aryl, especially phenyl, or C_{1-10} alkyl, especially methyl or ethyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a $(CR_{10}R_{20})_{n'}NHS(O)_2R_{18}$ group, R_{18} is suitably alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a optionally substituted aryl, the aryl is preferably phenyl. The aryl ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from C_{1-4} alkyl, halogen, especially fluoro or chloro, $(CR_{10}R_{20})_tOR_{13}$, (wherein t is 0, or an integer of 1 to 4), $-(CR_{10}R_{20})_tNR_{10}R_{20}$, especially amino or mono- or di-alkylamino $-(CR_{10}R_{20})_tS(O)_mR_{25}$, wherein m is 0, 1 or 2 ; - SH-, $-(CR_{10}R_{20})_n$-NR_8R_9, $-NR_{10}C(Z)R_8$ (such $-NHCO(C_{1-10}$ alkyl)); $-NR_{10}S(O)_mR_{25}$ (such as

-$NHSO_2(C_{1-10}$ alkyl)). Preferably the phenyl is substituted in the 3 or 4- position by -$(CR_{10}R_{20})_tS(O)_mR_{25}$, and R_{25} is preferably C_{1-10} alkyl, especially methyl.

When R_2 is an optionally substituted heteroaryl or heteroarylalkyl group the ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from one or more times, by C_{1-4} alkyl, halogen, especially fluoro or chloro, $(CR_{10}R_{20})_tOR_{13}$, -$(CR_{10}R_{20})_tNR_{10}R_{20}$, especially amino or mono- or di-alkylamino -$(CR_{10}R_{20})_tS(O)_mR_{25}$, wherein m is 0, 1 or 2 ; -SH-, -$(CR_{10}R_{20})_n$-NR_8R_9, -$NR_{10}C(Z)R_8$ (such -$NHCO(C_{1-10}$ alkyl)); -$NR_{10}S(O)_mR_{25}$ (such as -$NHSO_2(C_{1-10}$ alkyl)); t is 0, or an integer of 1 to 4.

One skilled in the art would readily recognize that when R_2 is a $(CR_{10}R_{20})_{n'}OC(Z)R_{13}$, or $(CR_{10}R_{20})_{n'}OC(Z)NR_8R_9$ moiety, or any similarly substituted group that n' is preferably at least 2 which will allow for the synthesis of stable compounds.

Suitably, R_3 is or Q-$(Y_1)_t$; and Q is an aryl or heteroaryl group. Preferably when Q is a heteroaryl moiety it is a 2- or 3-thiophene. Preferably R_3 is a substituted phenyl. More preferred Q is phenyl. Q is independently substituted 1 to 3 times by Y_1. Preferably t is 1 or 2. More preferably, when R_3 is mono-substituted phenyl, the substituent is located at the 4-position.

Preferably Q is substituted by 1 or 2 substituents which include halogen, C_{1-5} alkyl and -$(CR_{10}R_{20})_nY_2$ wherein Y_2 is -OR_8, -NO_2, -$S(O)_{m'}R_{11}$, -SR_8, -$S(O)_mNR_8R_9$; -NR_8R_9, -$O(CR_{10}R_{20})_nNR_8R_9$, -$C(O)R_8$, -$CO_2R_8$, -$CO_2(CR_{10}R_{20})_{n'}CONR_8R_9$, -CN; -$C(Z)NR_8R_9$, -$NR_{10}S(O)_mR_{11}$, -$NR_{10}C(Z)R_8$, -$NR_{10}C(Z)NR_8R_9$, -$C(Z)NR_8OR_9$, -$N(OR_{21})C(Z)NR_8R_9$, -$NR_{10}C(=NR_{15})NR_8R_9$, -$C(=NOR_{13})NR_8R_9$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl and 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl.

Preferred substituents Y_1 for use in R_3 when the aryl or heteroaryl group Q is mono-substituted include -$(CR_{10}R_{20})_nY_2$ wherein: n is 0, 1, 2 or 3, preferably 0 or 1; and Y_2 is -OR_8, especially where R_8 is hydrogen or C_{1-10} alkyl; -NO_2; -$S(O)_{m'}R_{11}$, especially where R_{11} is C_{1-10} alkyl; -SR_8, especially where R_8 is C_{1-10} alkyl; -$S(O)_mNR_8R_9$, especially where R_8 and R_9 is each hydrogen or C_{1-10} alkyl or R_8 and R_9 together with the nitrogen to which they are attached form a 5 to 7 membered ring which optionally includes another heteroatom selected from oxygen, sulfur or NR_{12} and m is 2; n' is 1 to 10; -NR_8R_9 , especially where R_8 and R_9 is each hydrogen, methyl or benzyl or R_8 and R_9 together with the nitrogen to which they are attached form a 5 to 7 membered ring which optionally includes another heteroatom selected from oxygen, sulfur or NR_{12}; -$O(CR_{10}R_{20})_nNR_8R_9$, especially where R_8 and R_9 is

each C_{1-10} alkyl; $-C(O)R_8$, especially where R_8 is hydrogen or C_{1-10} alkyl; $-CO_2R_8$, especially where R_8 is hydrogen or C_{1-10} alkyl; $-CO_2(CR_{10}R_{20})_n CONR_8R_9$, especially where R_8 and R_9 is hydrogen or C_{1-10} alkyl; -CN; $-C(Z)NR_8R_9$, especially where R_8 and R_9 is hydrogen or C_{1-10} alkyl; $-NR_{10}S(O)_mR_{11}$, especially where R_{10} is hydrogen or C_{1-10} alkyl and R_{11} is C_{1-10} alkyl or a halosubstituted ; $-NR_{10}C(Z)R_8$, especially where R_8 is C_{1-10} alkyl and R_{10} is hydrogen and Z is oxygen; $-C(Z)NR_8OR_9$, especially where R_8 and R_9 is each hydrogen and Z is oxygen; $-NR_{10}C(Z)NR_8R_9$, especially where R_8 and R_9 is each hydrogen or C_{1-10} alkyl and Z is oxygen; $-N(OR_{21})C(Z)NR_8R_9$, especially where R_8 especially where R_8, R_9 and R_{21} is each hydrogen or C_{1-10} alkyl and Z is oxygen; $-C(=NOR_{13})NR_8R_9$, especially where R_8, R_9 and R_{13} is each hydrogen; $-NR_{10}C(=NR_{15})NR_8R_9$, especially where R_8 and R_9 is hydrogen, C_{1-10} alkyl or arylalkyl and R_{15} is cyano; and 5-(R_{18})-1,2,4-oxadizaol-3-yl and 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially where R_{12} is hydrogen and R_{18} and R_{19} is each hydrogen or C_{1-10} alkyl or together are oxo.

Preferred substituents for use in R_3 when the aryl or heteroaryl group Q is disubstituted include those hereinbefore listed for use when Q is mono-substituted and, as further substituent(s), halogen and C_{1-10} alkyl. When R_3 is phenyl substituted with two or three substituents, the alkyl moieties preferably have from one to three carbons, more preferably one. Preferred ring positions for two substituents are the 3- and 4-positions and, for three substituents, the 3-, 4- and 5- positions. The substituent at the 3- and 5-positions is preferably C_{1-2} alkyl, such as methyl, or halogen, such as bromo, fluoro or chloro, while the substituent at the 4-position is preferably hydroxyl.

More preferably, for R_3 substituents wherein Y_1 is $(CR_{10}R20)_nY_2$, n is 0 or 1 and Y_2 is -OH, $-S(O)_m'R_{11}$, especially where R_{11} is C_{1-10} alkyl; $-SR_8$, especially where R_8 is C_{1-10} alkyl; $-NR_8R_9$, especially where R_8 and R_9 is hydrogen, alkyl, aryl alkyl, or aryl or R_8 and R_9 together with the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl or morpholinyl ring, more prefereably the R_8 and R_9 terms in the NR_8R_9 moiety are hydrogen, methyl or benzyl; $-CO_2R_8$, especially where R_8 is hydrogen or C_{1-10} alkyl; $-S(O)_m'NR_8R_9$, especially where R_8 and R_9 is each hydrogen or C_{1-10} alkyl; $-NR_{10}S(O)_mR_{11}$, especially where R_{10} is hydrogen and R_{11} is C_{1-10} alkyl or 5-(R_{18})-1,2,4-oxadizaol-3-yl and 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl, especially where R_{12} is hydrogen and R_{18} and R_{19} is hydrogen or C_{1-10} alkyl or together are oxo.

Most preferably, Y_1 is methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, N,N-dimethylaminomethyl, N-benzyl-N-methylaminomethyl,

N-morpholinomethyl, methanesulfonamido, sulphonamidomethyl, 5-methyl-4,5-dihydro-1,2,4-oxadiazol-3-yl or 5,5-dimethyl-4,5-dihydro-1,2,4-oxadiazol-3-yl.

In Formula (I), suitably R_4 is a halosubstituted phenyl, naphth-1-yl, or naphth-2-yl ring. Preferably R_4 is a halosubstituted phenyl, and preferably the halogen is fluorine, more preferably in the 4-position

A preferred grouping of formula (I) are those compounds wherein R_2 is an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7}cycloalkyl, or an optionally substituted C_{3-7}cycloalkyl C_{1-10} alkyl, an optionally substituted aryl, an optionally substituted heterocyclic alkyl, an optionally substituted heterocyclic, optionally substituted heteroaryl or heteroarylalkyl, $(CR_{10}R_{20})_{n'}OR_{13}$, $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$, $(CR_{10}R_{20})_{n'}NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$, or $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$; and R_1, R_3, and R_4 are as defined for Formula (I).

More preferred are those compounds wherein R_2 is a C_{1-4} alkyl (branched and unbranched), such as isopropyl, butyl, t-butyl, n-propyl, a methylthio propyl, a methylsulfinyl propyl, an amino propyl, N-methyl-N-benzylamino propyl group, (phenylmethyl)amino-1-propyl, diethylamino propyl, cyclopropyl methyl, morpholinyl butyl, morpholinyl propyl, morpholinyl ethyl, 1-Formyl-4-piperidinyl, 1-benzyl-4-piperidinyl, 1-methyl-4-piperidinyl, 1-ethoxycarbonyl-4-piperidinyl, phenyl substituted by halogen, thioalkyl or sulfinyl alkyl such as a methylthio, methylsulfinyl or methylsulfonyl moiety; and R_1, R_3, and R_4 are as defined for Formula (I).

Further preferred compounds of Formula (I) are those wherein R_1 is an optionally substituted 4-pyridyl or pyrimidinyl; and more preferably R_4 is a 2-methyl-4-pyridyl or 2-amino-pyrimidinyl.

Other groupings include those where R_2 is hydrogen, and R_3 is a 2- or 3-thiophene, or a substituted phenyl wherein the substituents are selected from methyl thio, methylsulfinyl, methylsulfonyl, methoxy, N-morpholinomethyl, $-CH_2NH_2$, or $-C(=NOH)NH_2$; provided that when R_4 is phenyl than the methylthio, methylsulfinyl, methylsulfonyl groups are in the 2- or 3- position of the phenyl ring; and R_4 is a halosubstituted phenyl, naphth-1-yl, or naphth-2-yl; or a phamaceutically acceptable salt thereof.

Most preferred are those compounds wherein R_2 is other than hydrogen, when R_4 is an unsubstituted 4-pyridyl and R_3 is substituted phenyl.

Exemplified compounds herein include:

4-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;

4-(1-Napthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(1-Napthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Napthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Napthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-1-methyl-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;
or pharmaceutically acceptable salts thereof.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent Y_1 in R_3 comprises a carboxy group. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quarternary ammonium cations.

The following terms, as used herein, refer to:

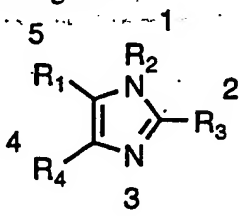
- "halo" - all halogens, that is chloro, fluoro, bromo and iodo;
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like;
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole;
- "heterocyclic" (on its own or in any combination, such as "heterocyclylalkyl") - a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine or pyrazolidine;
- "aroyl" - a C(O)Ar, wherein Ar is as phenyl, napthyl, or aryl alkyl derivatives, such as benzyl and the like;
- "alkanoyl" - a C(O)C_{1-10}alkyl wherein the alkyl is as defined above;
- "sulfinyl" - the oxide S(O) of the corresponding sulfide, while the term "thio" refers to the sulfide;
- The term "aralkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean an aryl, heteroaryl or heterocyclic moiety as respectively defined above said group connected to C_{1-6} alkyl group as also defined above unless otherwise indicated.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; S(O)m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; or where the R_7R_{17} may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10}

alkoxy, $S(O)_m$ alkyl, amino, mono & di-substituted amino, such as in the NR_7R_{17} group, C_{1-10} alkyl, or CF_3.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

For the purposes herein of nomenclature, the compounds of formula (I) are named by their position corresponding to:



Compounds of formula (I) are imidazole derivatives which may be readily prepared using procedures well-known to those skilled in the art, and described in, for instance, Comprehensive Heterocyclic Chemistry, ed Katritzky and Rees, Pergamon Press, 1984, **5**, 457-497, from starting materials which are either commercially available or can be prepared from such by analogy with well-known processes. A key step in many such syntheses is the formation of the central imidazole nucleus, to give compounds of formula (I). Suitable procedures are described in *inter alia* US patent nos. 3,707,475 and 3,940,486 which are herein incorporated by reference in their entirety. These patents describe the synthesis of a-diketones and a-hydroxyketones (benzoins) and their subsequent use in preparing imidazoles and N-hydroxyl imidazoles. Thereafter, further compounds of formula (I) may be obtained by manipulating substituents in any of the groups R_1, R_2, R_3 and R_4 using conventional functional group interconversion procedures.

In particular, in a first process, compounds of formula (I) may be prepared by condensing an α-diketone of formula (II):

$$R_1COCOR_4 \qquad (II)$$

wherein R_1 and R_4 are as hereinbefore defined, or an equivalent thereof, with an aldehyde of the formula (III):

$$R_3CHO \qquad (III)$$

wherein R_3 is as hereinbefore defined, or an equivalent thereof, and, if necessary, with ammonia or a source thereof, under imidazole-ring forming conditions.

Suitable equivalents of the α-diketone are well known to those skilled in the art and include the corresponding α-keto-oxime and α-dioxime. Suitable equivalents of the aldehyde of formula (III) are well known in the art and include the corresponding oxime and acetal.

Ammonia, or a source thereof, is preferably used in excess, with at least a dimolar amount being used in the case of the α-diketone and at least an equimolar amount in the case of the α-keto-oxime.

Suitable sources of ammonia include ammonium salts of organic carboxylic acids, such as an ammonium C_{1-6} alkanoate, for instance ammonium acetate and ammonium formate, preferably ammonium acetate, and carboxylic amides, in particular of formic acid, such as formamide. An ammonium salt is generally used in large excess and in the presence of an acid, such as a C_{1-6} carboxylic acid which acid may also be used as a solvent for the reaction. If formamide is used, this may be used in excess, as the reaction solvent. An alternative solvent such as ethanol or dimethyl sulphoxide (Lantos *et al*, J Het Chem, **19**, 1375, 1982) may be used. An additional solvent may also be employed, for instance, dimethyl formamide may be used with formamide. The reaction is generally carried out at elevated temperatures, for instance under reflux conditions, and if desired, in a sealed vessel optionally under pressure and/or an inert gas atmosphere, for instance nitrogen.

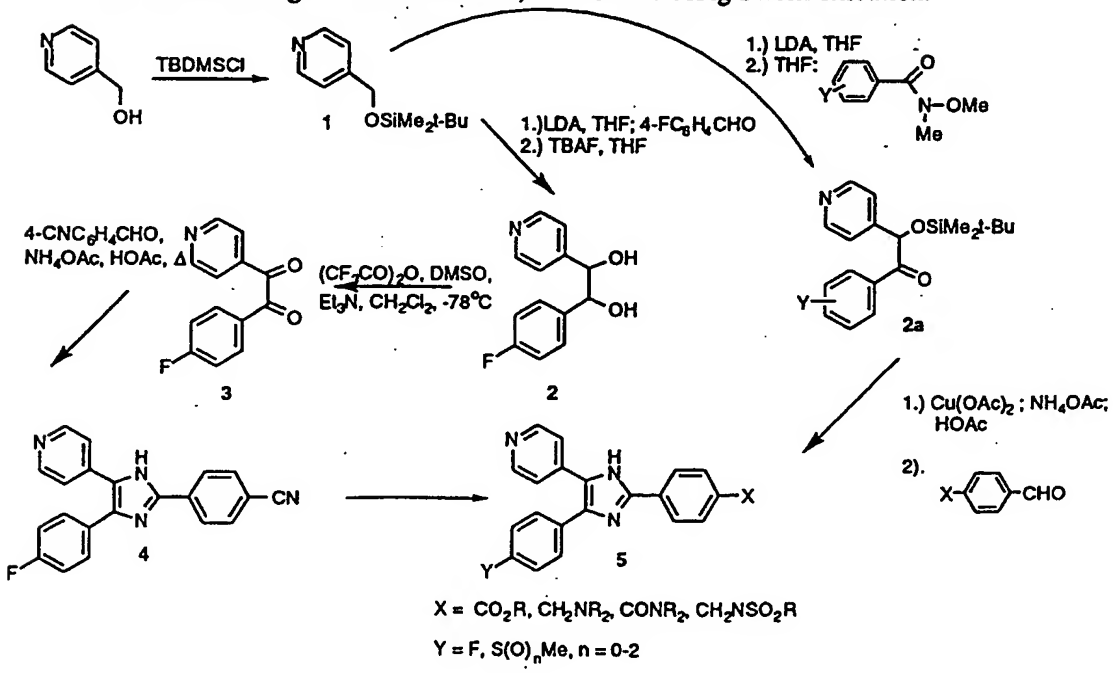
A further suitable source of ammonia is hydroxylamine, in which case the initially formed imidazole is an N-hydroxy-N-oxide imidazole. This may then be reduced to the corresponding N-hydroxy imidazole by treating with a suitable reducing agent such as sodium borohydride, in an appropriate solvent such as methanol, following the method of Akange and Allan, Chem and Ind, 5 Jan 1975, 38. The N-hydroxy imidazole may in turn be converted to an imidazole of formula (I) in which R_2 is hydrogen by treatment with a conventional deoxygenating agent such as phosphorus trichloride or a trialkylphosphite such as trimethyl- or triethyl-phosphite. N-hydroxy-N-oxide imidazoles may be readily obtained by treating an α-diketone of formula (II) with an aldehyde of formula (II) with about two equivalents of hydroxylamine or the corresponding aldoxime and about one equivalent of hydroxylamine, under proton catalysis. Alternatively, the N-oxide may be obtained by the acid catalysed condensation of the corresponding α-dioxime or α-keto-oxime with an aldoxime of the aldehyde of formula (III).

When the compound of formula (II) is an α-keto-oxime derivative, it will be appreciated that the product initially obtained will be a compound of formula (I) in which R_2 is hydroxyl which may be converted into a compound of formula (I) in which R_2 is hydrogen as described above.

It will be appreciated by those skilled in the art that in some instances, it will not be necessary to provide a separate source of ammonia as the α-diketone or aldehyde equivalent may already contain such a source. Examples of this include α-dioxime or α-keto-oxime and aldoxime.

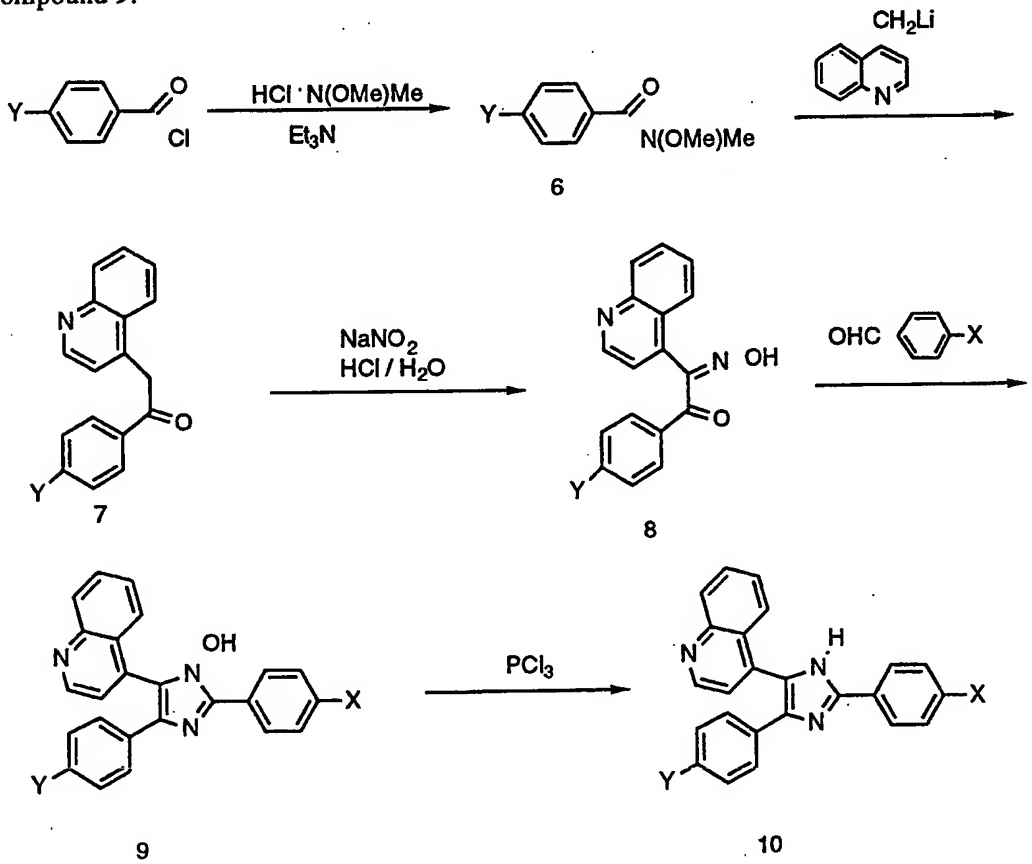
The compounds of formula (II) may be obtained by applying well-known synthetic procedures, some of which are illustrated in schemes I and II. Although these illustrate syntheses in which R_4 is either 4-pyridyl or 4-quinolinyl, they may be equally applied to any of the other heteroaryl rings within the definition of R_4 by appropriate choice of starting material.

In Scheme I, the anion prepared from 1, by treatment with a strong base such as lithium di-*iso*-propylamide, is condensed with a substituted benz-aldehyde, to give, after removal of the protecting group, the diol 2. This may then be converted to the a-diketone 3 by a Swern oxidation of which any number of potentially useful variations are known and may be used. The a-diketone 3 is then cyclised to an imidazole 4, a compound of formula (I), by heating 3 with a substituted benzaldehyde in a mixture of ammonium acetate, as the source of ammonia, and an appropriate solvent, for example acetic acid or DMSO. The imidazole 4 may then be transformed into other imidazoles 5 by appropriate functional group interconversion procedures. Scheme I also illustrates the preparation of a protected α-hydroxyketone 2a, by condensing the anion of 1 with an appropriately activated carbonyl derivative of a substituted benzamide, such as the N-methoxy-N-methylamide, to yield a protected a-hydroxyketone. This adduct 2a may then be directly converted to the imidazole 5, using a combination of a copper (II) salt, such as copper (II) acetate, as an oxidising agent and ammon-ium acetate as a source of ammonia. The α-hydroxyketone 2a may also be deprotected and then oxidised to give an a-diketone 3, for instance using Swern oxidation.



Scheme I

Scheme II illustrates the use of an a-keto-oxime for preparing a compound of formula (I). A heterocyclic ketone **7** is prepared by adding the anion of 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone **7**. The α-keto-oxime **8** is then prepared from **7** using standard conditions, such as reaction with sodium nitrite, and this may then be reacted with a benzaldehyde to afford an N-hydroxyimidazole **9**, a compound of formula (I) in which R_2 is hydroxy. This may converted to **10**, a further compound of formula (I) in which R_2 is hydrogen, by treating it with a deoxygenating agent such as phosphorus trichloride or a trialkyl phosphite, such as trimethyl or triethylphosphite. For compounds of formula (I) wherein R_3 is $-(CR_{10}R_{20})_n-P(Z)-(X_bR_{13})_2$, the reagent $OHC-(CR_{10}R_{20})_n-P(Z)-(X_bR_{13})_2$ may be used instead of $OHC-C_6H_4-X$ to make the appropriately substituted compound **9**.



Scheme II

In a further process, a compound of formula (I) may be obtained by treating an a-hydroxyketone compound of formula (IIA):

R'CHOHCOR" (IIA)

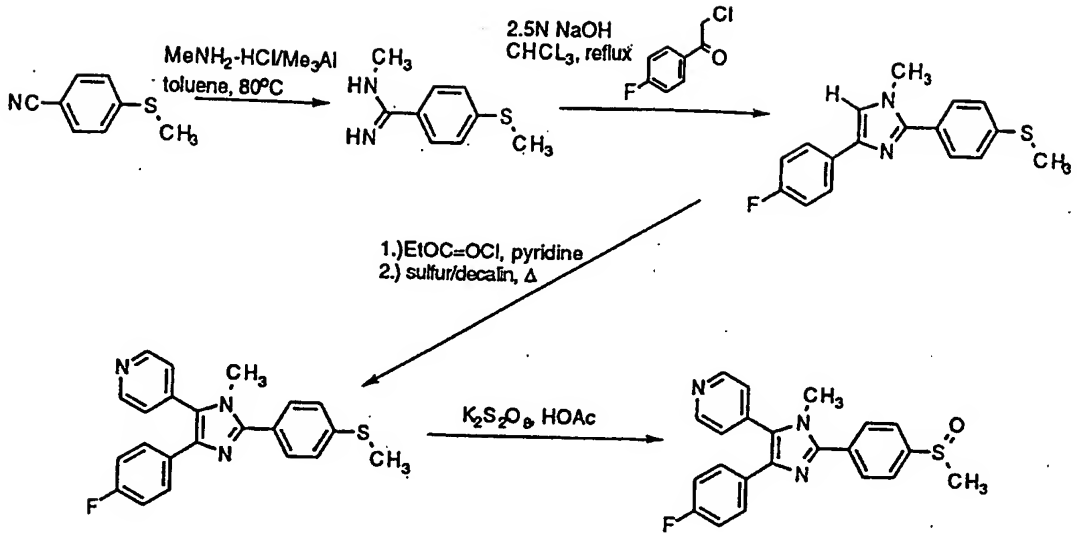
wherein one of R' and R" is R_1 and the other is R_4, a suitably protected derivative thereof or the a-hydroxy-oxime or a-haloketone derivative thereof, with an oxidising agent capable of converting said compound into the corresponding a-diketone, in the presence of an aldehyde of formula (III) or an equivalent thereof, and a source of ammonia. Suitable oxidising agents include, for example, an oxidising heavy metal salt, preferably an organic copper (II) salt, such as copper (II) acetate or copper (II) citrate. The reaction may be effected in a solvent such as acetic acid, under reflux conditions. Alternatively, a lower alkanol solvent, such as methanol or ethanol, may be used, preferably at a temperature in the region of from 30 to 100°C (see The Chemistry of Heterocyclic Compounds, Imidazole and its derivatives, part I, ed. Weissberger, Interscience Publishers, Inc., New York, 1953, 38). This approach is also illustrated in Scheme I.

In a further process, a compound of formula (I) may be obtained by treatment with a compound of formula (XI) as described later. A compound of Formula (XI) is obtained by treating a compound (an amidine) of formula (IV):

$R_3C(=NH)NHR_2$ (IV)

wherein R_2 and R_3 are as hereinbefore defined, or a salt thereof, with a reactive ester of an α-hydroxyketone of formula (IIA) or the corresponding α-haloketone, in an inert solvent such as a halogenated hydrocarbon solvent, for example chloroform, at a moderately elevated temperature and, if necessary, in the presence of a suitable condensation agent such as a base. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance, methane or *p*-toluene sulphonic acid. The amidine of formula (IV) is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ* , by employing a two phase system in which the reactive ester is in an inert organic solvent such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous stirring. Suitable amidines of formula (IV) may be obtained by standard methods, see for instance, Garigipati R, Tetrahedron Letters, 190, **31**, 1989.

Compounds of Formula (IV) wherein R_2 is methyl, for instance may be made by the route indicated below.



In a further process, a compound of formula (I) may be obtained by treating an iminoether of formula (V):

$$R_3C{=}NOR \qquad (V)$$

wherein R_3 is as hereinbefore defined and R is $C_{1\text{-}10}$ alkyl, aryl or aryl $C_{1\text{-}4}$ alkyl, with an α-aminoketone of the formula (VI):

$$R'CHNH_2COR'' \qquad (VI)$$

wherein one of R' and R" is R_1 and the other is R_4 in a suitable solvent.

In a further process, N-substituted compounds of formula (I) may be prepared by treating the anion of an amide of formula (VII):

$$R_1CH_2NR_2COR_3 \qquad (VII)$$

wherein R_1 and R_3 are as hereinbefore defined and R_2 is as hereinbefore defined other than hydrogen, with:

(a) a nitrile of the formula (VIII):

$$R_4CN \qquad (VIII)$$

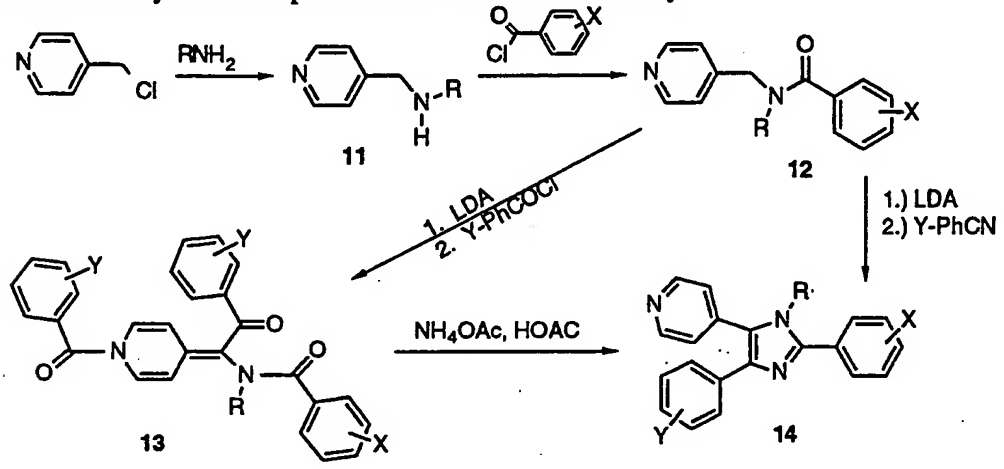
wherein R_4 is as hereinbefore defined, or

(b) an excess of an acyl halide, for instance an acyl chloride, of the formula (IX):

$$R_4COHal \qquad (IX)$$

wherein R_4 is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.

This approach permits the regiospecific preparation of compound of formula (I) substituted at the 1-position, as illustrated in Scheme III. A primary amine RNH_2 is treated with 4-chloromethylpyridine to give **11** which is then converted to the amide **12** by standard techniques. Deprotonation of **12** with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aroyl chloride yields the *bis*-acylated compound **13** which is then closed to an imidazole compound of formula (I), **14**, by heating in acetic acid containing ammonium acetate. Alternatively, the anion of **12** may be reacted with a substituted aryl nitrile to produce the imidazole **14** directly.



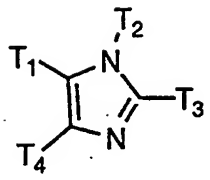
Scheme III

In a further process, compounds of formula (I) may be prepared by treating a compound of formula (X):

$$R'COCHR''X_cCOR_3 \qquad (X)$$

wherein R', R" and R_3 are as hereinbefore defined and X_c is O or NH, with a source of ammonia, as hereinbefore described, under imidazole ring forming conditions or cyclising the corresponding Schiff's base, formed by treating the compound of formula (X) in which X_c is NH with an amine R_2NH_2, for instance thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride (see Engel and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny *et al.*, J Org Chem, 1963, **28**, 3381). Compounds of formula (X) may be obtained, for instance, by acylating the corresponding a-keto-oxime (X_c is NH) or a-hydroxyketone (X_c is O) with an acyl halide of the formula R_3COHal wherein R_3 is as hereinbefore defined, or the corresponding anhydride, under standard acylating conditions.

In a further process, compounds of formula (I) may be prepared by coupling a suitable derivative of a compound of formula (XI):



(XI)

wherein: T_2 is a nitrogen protecting group or R_2, other than hydrogen; and T_1 is hydrogen, T_3 is Q and T_4 is R_4; T_1 is R_1, T_3 is hydrogen and T_4 is R_4; or T_1 is R_1, T_3 is Q and T_4 is hydrogen , in which R_1, R_2, R_3, R_4 and Q are as hereinbefore defined; with: (i) when T_1 is hydrogen, a suitable derivative of the heteroaryl ring R_1H, under ring coupling conditions, to effect coupling of the heteroaryl ring R_1 to the imidazole nucleus at position 5; (ii) when T_3 is hydrogen, a suitable derivative of the aryl or heteroaryl ring QH, under ring coupling conditions, to effect coupling of the ring Q to the imidazole nucleus at position 2; or (iii) when T_4 is hydrogen, a suitable derivative of the aryl ring R_4H, under ring coupling conditions, to effect coupling of the aryl ring R_4 to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of formula (XI), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of formula (XI) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is herewith incorporated.

Suitable organomagnesium and organozinc derivatives of a compound of formula (XI) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (O) or palladium (II) catalyst, following the procedure of Kumada *et al.*, Tetrahedron Letters, **22**, 5319 (1981). Suitable such catalysts include *tetrakis*-(triphenylphosphine)palladium and $PdCl_2$[1,4-*bis*-(diphenylphosphino)-butane], optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as Ni(II)Cl_2(1,2-biphenylphosphino)ethane, may also be used for coupling an aryl ring, following the procedure of Pridgen, J. Org.

Chem, 1982, **47**, 4319. Suitable reaction solvents include hexamethylphosphor-amide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable organomagnesium and organozinc derivatives may be obtained by treating a compound of formula (XI) or the bromo derivative thereof with an alkyllithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

A trialkyltin derivative of the compound of formula (XI) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis*-(triphenylphosphine)-palladium, by the method described in by Stille, J. Amer. Chem. Soc., 1987, **109**, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corres-ponding compound of formula (XI) with a lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of formula (XI) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of formula (XI) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of a catalyst such as *tetrakis*-(triphenyl-phosphine)-palladium, under conditions similar to those described above.

Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of formula (XI), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or $PdCl_2$[1,4-*bis*-(diphenylphosphino)-butane] in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, **84**, 439, 1965, Snieckus,V., Tetrahedron Lett., **29**, 2135, 1988 and Terashimia, M., Chem. Pharm. Bull., **11**, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about

100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al*, J Org Chem, **49**, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compunds of formula (XI). Thus, in general, amino and sulfur substituents should be non-oxidised or protected and the N-1 nitrogen of a compound of formula (XI) be protected, if an NH compound is finally required. Nitro, bromo, iodo and hydroxyl groups should preferably be avoided in compounds of formula (XI) in which T_1 is hydrogen.

Compounds of formula (XI) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of formula (I). In particular, an a-halo-ketone R_4COCH_2Hal (for compounds of formula (XI) in which T_1 is hydrogen) or R_1COCH_2Hal (for compounds of formula (XI) in which T_4 is hydrogen) may be reacted with an amidine of formula (IV) or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable a-halo-ketones is described in WO 91/19497. For a compound of formula (XI) in which T_3 is hydrogen, an a-diketone of formula (II) may be condensed with a formaldehyde or an equivalent thereof, in the presence of a source of ammonia. Suitable bromo derivatives of the compound of formula (XI) may be obtained by brominating the corresponding compound of formula (XI) under standard brominating conditions, for instance bromine in a solvent such as dichloromethane or THF.

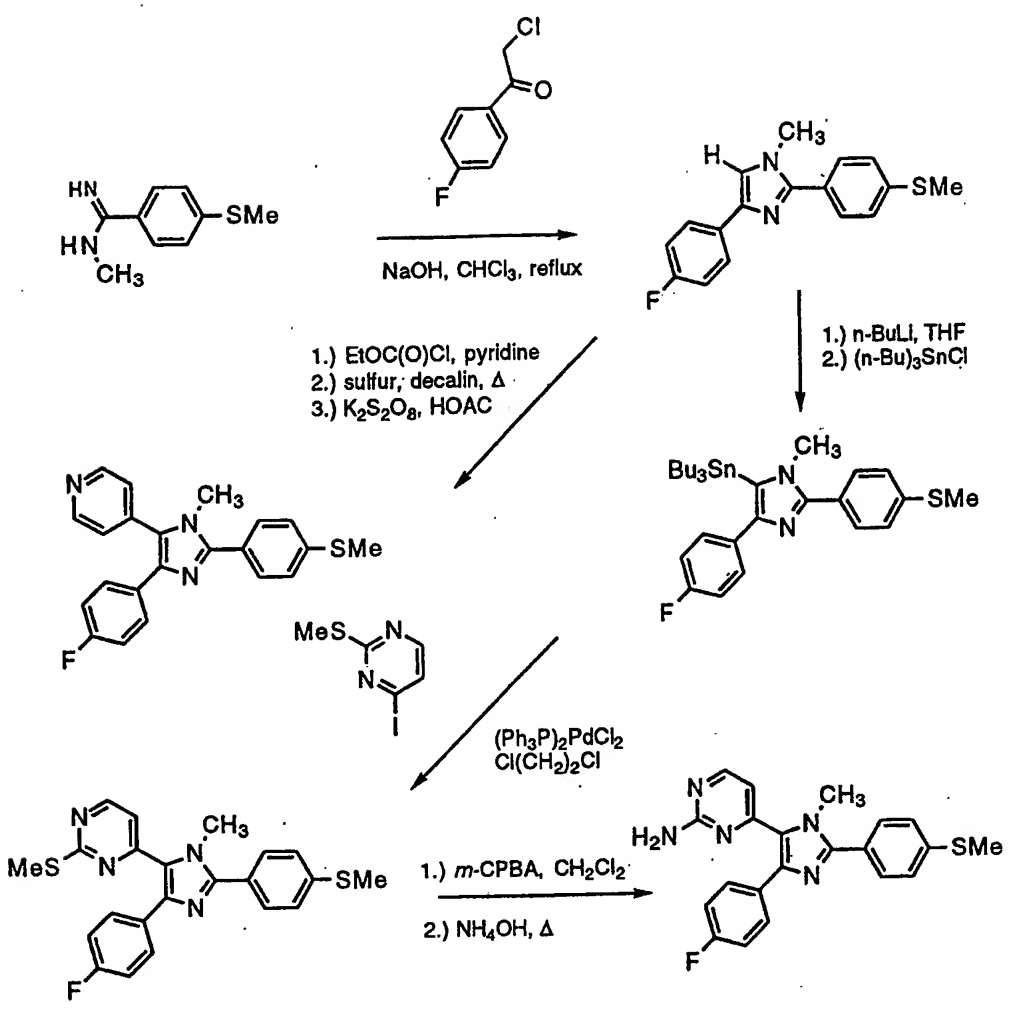
Compounds of formula (I) may also be prepared by a process which comprises reacting a compound of formula (XI), wherein T_1 is hydrogen, with an N-acyl heteroaryl salt, according to the method disclosed in US patents 4,803,279, 4,719,218 and 5,002,942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be subjected to oxidative-deacylation conditions. The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a solution of the compound of formula (XI) in the heteroaryl compound R_1H or in an inert solvent such as methylene chloride to which the heteroaryl compound has been added. Suitable deacylating and oxidising

conditions are described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942, which references are hereby incorporated in their entirety. Suitable oxidising systems include sulfur in an inert solvent or solvent mixture, such as decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or, preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.

Once the imidazole nucleus has been established, further compounds of formula (I) which may be prepared by applying standard techniques for functional group interconversion, for instance: -C(O)NR_8R_9 from -CO_2CH_3 by heating with or without catalytic metal cyanide, e.g. NaCN, and HNR_8R_9 in CH_3OH; -OC(O)R_8 from -OH with e.g.,ClC(O)R_8 in pyridine; -NR_{10}-C(S)NR_8R_9 from -NHR_{10} with an alkylisothiocyante or thiocyanic acid; $NR_6C(O)OR_6$ from -NHR_6 with the alkyl chloroformate; -$NR_{10}C(O)NR_8R_9$ from -NHR_{10} by treatment with an isocyanate, e.g. HN=C=O or $R_{10}N$=C=O; -NR_{10}-C(O)R_8 from -NHR_{10} by treatment with Cl-C(O)R_8 in pyridine; -C(=NR_{10})NR_8R_9 from -C(NR_8R_9)SR_8 with $H_3NR_8^+OAc^-$ by heating in alcohol; -C(NR_8R_9)SR_8 from -C(S)NR_8R_9 with R_6-I in an inert solvent, e.g. acetone; -C(S)NR_8R_9 (where R_8 or R_9 is not hydrogen) from -C(S)NH_2 with HNR_8R_9, -C(=NCN)-NR_8R_9 from -C(=NR_8R_9)-SR_8 with NH_2CN by heating in anhydrous alcohol, alternatively from -C(=NH)-NR_8R_9 by treatment with BrCN and NaOEt in EtOH; -NR_{10}-C(=NCN)SR_8 from -NHR_{10} by treatment with $(R_8S)_2C$=NCN; -$NR_{10}SO_2R_8$ from -NHR_{10} by treatment with $ClSO_2R_8$ by heating in pyridine; -$NR_{10}C(S)R_8$ from -$NR_{10}C(O)R_8$ by treatment with Lawesson's reagent [2,4-*bis*(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; -$NR_{10}SO_2CF_3$ from -NHR_6 with triflic anhydride and base; -$NR_{10}C(O)$-C(O)-OR_8 from -NHR_{10} with, e.g. methyloxalyl chloride and a base such as triethylamine; -$NR_{10}C(O)$-C(O)-NR_8R_9 from -$NR_{10}C(O)$-C(O)-OR_8 with HNR_8R_9; and 1-(NR_{10})-2-imidazolyl from -C(=NH)NHR_{10} by heating with 2-chloroacetaldehyde in chloroform (wherein R_6, R_8, R_9 and R_{10} are as hereinbefore defined).

Compounds of formula (I) in which R_2 is hydrogen may be readily converted into further compounds of formula (I) in which R_2 is other than hydrogen, for instance alkyl, by conventional procedures such as alkylation or acylation followed by reduction. Such methods are in general relatively inefficient as they lack regiospecificty and the desired N-1 product has to be separated from the mixture of N-1 and N-3 products. for instance by chromatography or fractional crystallisation.

Compounds of Formula (I) wherein R_2 is methyl and R_1 is 4-pyridyl or 4-(2-amino)pyrimidinyl for example may be made by the route indicated below.



Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, $(CR_{10}R_{20})_{n'}$ as defined in Formula (I). Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

It should be noted that the compounds of Formula (I),where R_4 may be an alkylsulfinyl, arylsulfinyl, alkylsulfonyl, or arylsulfonyl are prodrugs which are reductively converted in vivo to the corresponding alkylthio or arylthio form.

Pharmaceutically acid addition salts of compounds of formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Synthetic Examples

Example 1

2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole

a) To a solution of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole (4.5 g, 13.2 mmol) [See 1(b) below] in DMF (50 mL) was added triethyl phosphite (3.4 mL, 20 mmol), and the resulting mixture was heated at 100 °C for 2 h. After cooling, the mixture was poured into H_2O, and the solid which formed was collected by filtration, washed with H_2O and dried *in vacuo* to afford the title compound (4.0 g, 89%). Recrystallization from CH_2Cl_2/MeOH gave white solid with a mp of 268-269 °C.

b) **2-(4-Cyanophenyl)-4-(4-fluorophenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole** The title compound was prepared using the same procedure (US 3,940,486) employed to prepare 2-(t-butyl)-4-(phenyl)-N-1-hydroxy-5-(4-pyridyl)imidazole, except using 4-fluoro-2-hydroxyimino-2-(4-pyridyl)acetophenone and 4-cyanobenzaldehyde: ^1H NMR ($CDCl_3$): d 8.27 (d, 2H); 7.94 (d, 2H); 7.72 (d, 2H); 7.35 (d, 2H); 7.30 (dd, 2H); 6.96 (t, 2H).

Example 2

4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

(a) 1-(t-Butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone To a -20 °C solution of diisopropylamine (64.4 mL, 0.46 mol) and THF (120 mL) was added 207.8 mL (0.52 mol, 2.5 M solution in hexanes) of n-butyllithium dropwise over 15 min. The temperature was lowered to -15 °C and the mixture was stirred for 0.5 hr. The solution was cooled to -20 °C and 98.14 g (0.44 mol) of 4-(t-butyldimethylsilyloxy)methyl pyridine was added dropwise over 20 min. After stirring at -20°C for 45 min, a solution of 4-fluoro-N-methoxy-N-methylbenzamide (84.5 g, 0.46 mol) [See Ex. 10, step (a)] in THF (90 mL) was added dropwise over 0.5 hr. Once the addition was complete, the ice bath was removed and the reaction mixture was warmed to 0 °C for 1 hr, then stirred at rt for 1.5 hr. The mixture was poured into a solution of NH_4Cl (98 g) and H_2O (500 mL), then extracted with EtOAc (3 x 250

mL). The EtOAc extracts were washed with H_2O and saturated NaCl, then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded the title compound as an amber oil (114.2 g, 75%).

(b) 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

To a solution of 1-(t-butyldimethylsilyloxy)-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone (6.3 g, 18.3 mmol) in glacial acetic acid (125 mL) was added anhydrous copper (II) aetate (6.6 g, 36.5 mmol), ammonium acetate (14 g, 183 mmol) and 4-(methylthio)benzaldehyde (3.5 g, 22.9 mmol) and the mixture was heated at reflux. After 1 hr, the reaction was cooled then poured into a mixture of conc. NH_4OH (175 mL), ice (100 mL) and EtOAc (100 mL). The resulting mixture was stirred for 15 min, then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined EtOAc extracts were washed with saturated NaCl and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave an oil which was taken up in acetone. 3 N HCl was added dropwise to adjust the pH to 2-3; and the resulting solid was filtered. The title compound was isolated as the yellow hydrochloride salt (3.7 g, 51%).

Example 3

4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

To a solution of 4-(4-fluorophenyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole (0.80 g, 2.2 mmol) [See Ex. 2 above] in glacial acetic acid (15 mL) was added a solution of $K_2S_2O_8$ (0.72 g, 2.6 mmol) in H_2O (20 mL). Additional glacial acetic acid (15 mL) was added to ensure homogeneity, and the resulting solution was stirred at rt for 18 h. The mixture was then poured into H_2O, and the pH was adjusted to neutral by the addition of conc. NH_4OH. The solid which formed was collected by filtration to afford the title com-pound (0.65 g, 78%) as a tan solid, which was recrystallized from MeOH: mp 250-252 °C.

Example 4

4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole

To a solution of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole (3.7 g, 9.8 mmol) [See Ex. 3 above] in 1:10 3 N HCl/H_2O (88 mL) was added a solution of $KMnO_4$ (1.5 g, 9.8 mmol) in H_2O (15 mL). After stirring at rt for 1 h, additional $KMnO_4$ (0.15 g, 0.9 mmol) was added, and stirring was continued for 15 min. The mixture was then poured into saturated aqueous Na_2SO_3 (200 mL), and the pH was adjusted to slightly acidic by the addition of 3 N HCl, then to neutral by the addition of 2.5 N NaOH. The solid which formed was collected by filtration,

washed successively with H_2O and MeOH and recrystallized three times from MeOH to afford the title compound (0.63 g, 16%): mp 148-149 °C.

Example 5

4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2(b), except using 3-(methylthio)-benzaldehyde.

Example 6

4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 3, except using 4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

Example 7

4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2, except using 4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole.

Example 8

4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2 (b), except using 2-(methylthio)-benzaldehyde.

Example 9

4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 3, except using 4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

Example 10

4-(4-Fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2, except using 4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole.

Example 11

4-(4-Fluorophenyl)-2-(thiophen-2-yl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2(b), except using 2-thiophene carboxaldehyde.

Example 12

4-(4-Fluorophenyl)-2-(thiophen-3-yl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 81(b), except using 3-thiophene carboxaldehyde.

Example 13

4-(naphth-1-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2 (a), except using 1-naphth-(N-methoxy-N-methyl)amide.

Example 14

4-(naphth-2-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2(a), except using 2-naphth-(N-methoxy-N-methyl)amide.

Example 15

4-(naphth-1-yl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 3, except using 4-(naphth-1-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

Example 16

4-(naphth-2-yl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 3, except using 4-(naphth-2-yl)-2-(4-methylthiophenyl)-5-(4-pyridyl)-1H-imidazole.

Example 17

2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole

The title compound was prepared using the same procedure as described in Example 2 (b), except using 4-cyanobenzaldehyde, mp 268-269.

Example 18

2-(4-Aminomethylphenyl)-4-phenyl-5-(4-pyridyl)-imidazole

To a solution of 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-imidazole (2.5 g, 7.3 mmol) [See Ex. 17 above] in THF (50 mL) was added $LiAlH_4$ (7.3 mL of 1 M solution in THF, 7.3 mmol), and the resulting mixture was heated at reflux for 2 h, at which time tlc analysis indicated that the reaction was incomplete. Additional $LiAlH_4$ (4.0 mL, 4.0 mmol) was added and heating was continued for 30 min. The mixture was allowed to cool, then poured into 2.5 N NaOH and extracted with THF. The organic extract was washed with saturated aqueous NaCl and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 9:1 $CHCl_3$/MeOH, followed by 90:10:1 $CHCl_3$/MeOH/NH_3. The material that was isolated was triturated with Et_2O to afford the title compound (1.5 g, 60%): mp 214-215 °C.

Example 19

2-(4-Biotinamidomethylphenyl)-1-methyl-4-phenyl-5-(4-pyridyl)-imidazole

To a solution containing 2-(4-Aminomethylphenyl)-4-phenyl-5-(4-pyridyl)-imidazole (1 equivalent) in DMF was added N-hydroxysuccinimide biotin (1.2 eq). Follwing normal workup and chromatography the title compound was obtained: CIMS (NH_3, *m/z*): 523 (M^++H).

Example 20

4-(4-Fluorophenyl)-1-methyl-2-(4-methylsulfinyl)phenyl-5-(4-pyridyl)imidazole

(a) N-Methyl-4-(methylthio)phenyl benzamidine - The title compound was prepared following the procedure fo Garigipati (*Tetrahedron Lett.* **1990**, 31(14), 1969) except using methylamine hydrochloride and 4-(methylthio)-benzonitrile.

(b) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenylimidazole - The title compound was prepared following the procedure of Fitzi (U. S. Patent 3,940,486) except using N-methyl-4-(methio)phenylbenzamidine and 2-chloro-4'-fluoroacetophenone.

(c) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-(4-pyridyl)imidazole -The title compound was prepared by the procedure of Lantos et al. (*J. Org. Chem.* **1988**, 53, 4223) except using 4(4-fluoro)phenyl-1-methyl-2-(4-methylthio)phenylimidazole.

(d) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylsulfinyl)phenyl-5-(4-pyridyl)imidazole - The title compound was prepared by the same procedure as

described in Example 20 except usuing 4-(4-fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-(4-pyridyl)imidazole: CIMS (NH_3; m/z): 392 ($M^+ + H$).

Example 21

4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-amino)-pyrimidinyl]imidazole

(a) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methythio)phenyl-5-tri-n-butylstannylimidazole - The title compound was prepared by the procedure of Bender et al. (U. S. Patent 5,145,858 & US 5,002,941) except using 4-(4-fluoro)phenyl-1-methyl-2-(4-methylthio)phenylimidazole.

(b) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-methylthio)pyrimidinyl]imidazole - A mixture of 4-(4-Fluoro)phenyl-1-methyl-2-(4-methythio)phenyl-5-tri-n-butylstannylimidazole (0.25 g, 0.42 mmol), 4-iodo-2-methythiophenylpyrimidine (0.16 g, 0.63 mmol) [prepared by the procedure of Majeed et al. (*Tetrahedron* **1989**, 45(4), 993)] and bis(triphenylphosphine)-palladium(II) dichloride (0.30 g, 0.42 mmol) in 1,2 dichloroethane (10 mL) was heated to reflux for 24 h. The reaction mixture was cooled to ambient temperature and a solution of saturated potassium fluoride in methanol (2 mL) was added. After stirring for 1 h at ambient temperature, the mixture was poured into water and extracted twice with dichloromethane. The organic layers were combined, washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography eluting with dichloromethane to afford the title compound as a yellow foam (0.14 g, 78%).

(c) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylsulfonyl)phenyl-5-[4-(2-methylsulfonyl)pyrimidinyl]imidazole - To a solution of 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-methylthio)pyrimidinyl]imidazole (0.10 g, 0.24 mmol) in dichloromethane (10 mL) was added 80% *m*-chloroperbenzoic acid (0.25 g, 1.2 mmol). After stirring at ambient temperature for 18 h, the reaction mixture was poured into saturated aqueous sodium carbonate and the layers were separated. The organic phase was washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography eluting successively with dichloromethane and 1% methanol in dichloromethane to afford the title compound as a yellow foam (0.11 g, 94%).

(d) 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylthio)phenyl-5-[4-(2-amino)pyrimidinyl]imidazole - 4-(4-Fluoro)phenyl-1-methyl-2-(4-methylsulfonyl)-phenyl-5-[4-(2-methylsulfonyl)pyrimidinyl]imidazole (0.50 g, 0.10 mmol) was added to concentrated ammonium hydroxide (2 mL) and reaction mixture was heated to

150°C in a sealed vessel. After cooling to ambient temperature, the reaction mixture was diluted with water and extracted twice with dichloromethane and once with 4% methanol in dichloromethane. The organic layers were combined and the solvent evaporated. The residue was purified by flash chromatography eluting successively with 2%, 4% and 10% methanol in dichloromethane followed by trituration with ether to afford the title compound as a white solid (0.017 g, 39%): CIMS (NH_3, m/z): 424 ($M^+ + H$).

The following compounds may be made by analagous methods to those described above:

Example 22 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;

Example 23 4-(4-Fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;

Example 24 4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholino-propyl)-5-(4-pyridyl)imidazole;

Example 25 4-(4-Fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholino-methyl]phenyl)-5-(4-pyridyl)imidazole;

Example 26 4-(4-Fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholino-methyl]phenyl)-5-(4-pyridyl)imidazole;

Example 27 4-(4-Fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholino-methyl]phenyl)-5-(4-pyridyl)imidazole.

METHODS OF TREATMENT

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacutre of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine producution by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of formula Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interferring amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In particular, compounds of Formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic ß cells and Alzheimer's disease.

In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, the lentivirus infections such as equine infectious anaemia virus, caprine arthritis virus, visna virus, or the maedi virus, or the retroviruses, such as feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus.

The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of formula Formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils

into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutophil infiltration.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels; so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-8 or TNF; or (iii) the presence of IL-1, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-8 and TNF is based upon the effects of the compounds on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-6, IL-1, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event; or

d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease stated mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce

them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphoctye cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF–α) and Tumor Necrosis Factor beta (TNF-ß).

As used herein, the term "cytokine interfering" or "cytokine suppresive amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF-ß (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-ß are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), or pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (Ib) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These

procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also

include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan esteror a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formua (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total

body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

Interleukin-1 (IL-1)

Human peripheral blood monocytes were isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al*, J Immunol, **132**, 936 (1984). These monocytes ($1x10^6$) were plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle washing. Test compounds were then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures were incubated at 37°C for an additional 24h. At the end of this period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, **84**, 85, (1985) (based on ability of IL-1to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, **6** (1), 1-12 (1990) (ELISA assay). Compounds of formula (I) were shown to be inhibitors of *in vitro* IL-1 produced by human monocytes.

Tumor Necrosis Factor (TNF)

Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, J Immunol, **132**(2), 936 (1984). The monocytes were plated at a density of $1x10^6$ cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells were incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose ranges (compounds were solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concen-tration in the culture medium was 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopoly-saccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) was then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO_2 incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant was then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, J Immunol, 1991, **147**, 4307. Compounds of formula (I) were shown to be inhibitors of *in vitro* TNF production.

IL-1 and TNF inhibitory activity does not seem to correlate with the property of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition, further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-toxic doses.

Interleukin- 8 (IL-8)

Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) were maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells were then diluted 20-fold before being plated (250µl) into gelating coated 96-well plates. Prior to use, culture medium was replaced with fresh medium (200µl). Buffer or test compound (25µl, at concentrations between 1 and 10µM) was then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO_2. At the end of the incubation period, supernatant was removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from

R&D Systems (Minneapolis, MN). All data were presented as mean value (ng/ml) of multiple samples based on the standard curve. IC_{50}'s where appropriate were generated by non-linear regression analysis. The compounds of formula (I), examples 5, 8b and 9, demonstrated a dose dependent reduction in the production of IL-8 (a 50-65% inhibition of IL-8).

Cytokine Specific Binding Protein Assay (CSPB)

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible binding assay was developed using soluble cystosolic fraction from THP.1 cells and a radiolabeled compound. For instance, a suitable radiolabeled compound of the CSAID™ cytokine inhibitor class herein is 4-(Fluorophenyl)-2-(4-hydroxyphenyl-3,5-t_2)-5-(4-pyridyl)imidazole. In brief, the THP.1 cytosol was routinely prepared from cell lysate obtained by nitrogen cavitation followed by a 10 K x g low speed and a 100 K x g high speed centrifugation, the supernatant of which was designated as the cytosolic fraction. THP.1 cytosol was incubated with appropriately diluted radioligand at room temperature for a pre-determined time to allow the binding to achieve equilibrium. The sample was added to a G-10 column and eluted with 20 mm TRN, 50mMb - mercaptoethanol, NaN_3. The fraction encompassing the void volume was collected and the radioactivity was assessed by liquid scintillation counting. This was determined to reflect bound radioligand since the radioactive signal was abrogated by the presence of excess cold ligand in the incubation mixture or when there was no cytosolic fraction present. Compounds of Formula (I) at various doses were added to the binding assay to achieve inhibition of binding of the radiolabel. IC_{50}s as well as Ki values were determined by regression analysis and scatchard plot analysis respectively. There is generally excellent correlation between the IC_{50} of compounds tested in both the binding assay and the bioassay and can be used interchangeably in many cases.

Patent Application USSN 08/123175 Lee et al., filed September 1993 whose disclosure is incorporated by reference herein in its entirey describes the above noted method for screening drugs to identify compounds which interact with and bind to the CSBP. However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on

the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the cytokine specific binding protein may be employed in the creening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

More specifically, the Binding Assay is performed as follows:

MATERIALS:

Incubation buffer: 20 mM Tris, 1 mM $MgCl_2$, 20 mM Hepes, 0.02% NaN_3, store at 4°C. Elution buffer: 20 mM Tris, 50 mM 2-mercaptoethanol, NaN_3, store at 4°C.

G-10 Sephadex: add 100 g Sephadex G-10 (Pharmacia, Uppsala, Sweden) to 400 mL dd H_2O and allow to swell at room temperature for 2 hours. Decant fines and wash 3 times. Add NaN_3 and qs with dd H_2O to 500 mLs and store at 4°C.

Assemble Columns: Straw column, filter frit and tip (Kontes, SP 420160-000, 420162-002). Lowsorb tubes (Nunc) used in binding reaction. THP.1 cytosol spun at 15000 rpm for 5 min to clarify. THP.1 cytosol prepared by hypnotic treatment of cells and lysis by decompression in nitrogen. Nuclei and membrane fragments removed by differential centrifugation (10,000 g for 1 hour and 100,000 g for 1 hour).

Compounds: Non-radioactive Compound I with corresponding EtOH control (dilutions made in incubation buffer) and ^{3}H-Compound I (dilutions in incubation buffer)

METHOD:

A. Column Preparation
   1. Begin 30 min before anticipated elution of reaction mixture.
   2. Add 3 mL of G-10 slurry to column for bed vol of 1.5 ml.
   3. Rinse with 7 mL elution buffer (fill to top of column)
   4. Cut columns down to size.

B. Sample Incubation
   1. 15 min incubation at 4°C.
   2. Binding reaction mixture; 100 µL cytosol, 10 uL cold Compound I or EtOH control, 10 µL ^{3}H-Compound I (molar concentration depends on nature of study).
   3. "Free" control = 100 µL incubation buffer in lieu of cytosol preparation.

C. Sample Elution
   1. Elute at 4°C.

2. Add total reaction volume to G-10 column.
3. Add 400 µL elution buffer to column and discard eluate.
4. Add 500 µL elution buffer to column, collecting eluted volume in 20 ml scintillation vial.
5. Add 15 mL Ready Safe scintillation fluid.
6. Vortex and count in liquid scintillation counter for 5 minutes. Include a "total input counts control" (10 µL of labeled ligand).

D. Data Analysis

1. Plot DPMS as ouptut in graphic form and analyze by regression analysis and "Lundon ligand binding" software for the determination of IC 50 and Kd/Ki respectively.
2. Rank order the IC50s of the tested compounds in the bioassay and compare to that generated by the binding assay and establish a correlation curve.

The binding assay was further validated by the following criteria that THP.1 cytosol demonstrated saturable and specific binding of the radiolabeled compound.

Preparation of 4-(Fluorophenyl)-2-(4-hydroxyphenyl-3,5-t_2)-5-(4-pyridyl)imidazole, (Compound I).

A 2.9 mg (0.0059 mmol) portion of 2-(3,5-Dibromo-4-hydroxyphenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, Compound I(p), was dissolved in 0.95 mL of dry DMF and 0.05 mL of triethylamine in a 2.4 mL round bottom flask equipped with a small magnetic stirring bar. A 1.7 mg portion of 5% Pd/C (Engelhard lot 28845) was added, and the flask was attached to the stainless steel tritium manifold. The mixture was degassed through four freeze-pump-thaw cycles, then tritium gas (5.3 Ci, 0.091 mmol) was introduced. The reaction mixture was allowed to warm to room temperature and was stirred vigorously for 20h. The mixture was frozen in liquid nitrogen, the remaining tritium gas (2.4 Ci) was removed, and the flask was removed from the manifold. The reaction mixture was transferred, using 3 x 1 mL of methanol as rinsings, into a 10 mL round bottom flask, and the solvents were removed by static vacuum transfer. A 1.5 mL portion of methanol was added to the residue, then removed by static vacuum transfer. The latter process was repeated. Finally, the residue was suspended in 1.5 mL of ethanol and filtered through a syringe-tip Millipore filter (0.45 micron), along with 3 x ca. 1 mL ethanol rinsings. The total filtrate volume was determined to be 3.9 mL, and the total radioactivity, 94.2 mCi. Solution was determined to be 3.9 mL, and the total radioactivity, 94.2 mCi. HPLC analysis of filtrate (Partisil 5 ODS-3, 4.6 mm I.D. x 25 cm, 1 mL/min of 70:30:01 water/acetonitrile/trifluoroacetic acid, Radiomatic

Flo-One Beta radio detector with 3 mL/min of Ecoscint-H cocktail through a 0.75 mL cell) showed the presence of Compound I (R_t = 60 min. ca. 37% of total radioactivity), and a discrete intermediate presumed to be the monobromo derivative Compound Ia (R_t = 11.8 min, ca. 9%).

The filtrate solution was evaporated to near dryness with a stream of nitrogen, and the residue was dissolved in about 1.2 mL of the HPLC mobile phase. The solution was separated by HPLC as shown below, and the peaks corresponding to Compounds I and Ia and SB collected separately.

HPLC Method

Column	Altex Ultrasphere 10 mm I.D. x 25 cm
Mobile Phase	70:30:0.1 water/acetonitrile/trifluoroacetic acid
Flow Rate	5 mL/min
UV detection	210nm
Injection Volumes	0.05 - 0.4 m:
Retention Times	7.8 min Compound I 24 min Compound Ia

The pooled Compound I fractions totaled 32 mL in volume and the radioactive concentration was 1.52 mCi/mL (total 48.6 m Ci). The pooled SB Compound Ia [^{3}H] fractions (totaling 10.1 mCi) were evaporated to dryness and the residue was transferred quantitatively into a glass vial using 3.8 mL of absolute ethanol for further analysis.

An 8 mL (12.2 mCi) portion of Compound I was evaporated to dryness *in vacuo* at <35°C, then redissolved in 0.5 mL of mobile phase. The whole volume was injected into the HPLC system described above, and the appropriate peak was collected. Evaporation of the collected eluate *in vacuo* at <35°C and transfer of the yellow residue into a vial with absolute ethanol provided a solution (3.8 mL, 2.44 mCi/mL) of Compound I. The portion of this solution used for NMR analyses was first evaporated to dryness using stream of nitrogen then taken up in CD_3OD.

Analysis of 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl-3,5-t_2)-5-(4-pyridyl)imidazole, Compound I.

Radiochemical Purity by HPLC Method

Column	Ultrasphere Octyl, 5mm, 4.6 mm I.D. x 25 cm, Beckman
Mobile Phase	350:150:0.5(v/v/v) water/acetonitrile/trifluoroacetic acid
Flow Rate	1.0 mL/min
Mass detection	UV at 210 nm
Radioactivity detection	Ramona-D radioactivity flow detector
Scintillator	Tru-Count (Tru-Lab Supply Co.)
Flow rate	5.0 mL/min
Cell volume	0.75 mL
Retention time	7.7 min

Result	98.7

Radioactive Concentration by Scintillation Counting

Method	
Scintillator	Ready Safe (Beckman Instruments, Inc.)
Instrument	TM Analytic model 6881
Efficiency	Automated DPM calculation from quench curve
Result	2.44 mCi/mL

Specific Activity by Mass Spectrometry

Method	CI-MS, NH_3 reagent gas	
Result	20.0 Ci/mmol	
	^3H Distribution:	
	Unlabeled	44%
	Single Label	43%
	Double Label	13%

^3H NMR[9]

Method	
Instrument	Brunker AM 400
Experiment	Proton decoupled ^3H NMR Proton non-decoupled ^3H NMR Proton non-decoupled ^3H NMR
Peak Referencing	Solvent Peak of methanol ∂ 3.3
Solvent	Methanol-d_4
Result	Tritium is incorporated exclusively on the carbon atoms ortho to aromatic hydroxyl group

Analytical Summary

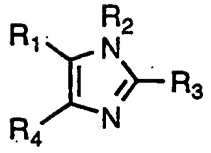
Assay	Result
Radiochemical purity determined by HPLC	98.7%
Radioactivity concentration determined by scintillation counting	2.44 mCi/mL
Specific activity determined by mass spectrometry	20.0 Ci/mmol
^3H NMR	agrees with the proposed structure

Representative compounds of Formula (I), Examples 1 to 21 herein have all demonstrated positive inhibitory activity in this binding assay.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is

1. A compound of the formula:



wherein:

R_1 is 4-pyridyl, pyrimidinyl, or quinolyl, which is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, C_{1-4} alkoxy, C_{1-4} alkylthio, $NR_{10}R_{20}$, or N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_2 is an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7}cycloalkyl, or an optionally substituted C_{3-7}cycloalkyl C_{1-10} alkyl, an optionally substituted aryl, an optionally substituted heterocyclic alkyl, an optionally substituted heterocyclic, optionally substituted heteroaryl or heteroarylalkyl, $(CR_{10}R_{20})_{n'}OR_{13}$, $(CR_{10}R_{20})_{n'}S(O)_mR_{25}$, $(CR_{10}R_{20})_{n'}NR_8R_9$, $(CR_{10}R_{20})_{n'}C(Z)OR_{13}$, $(CR_{10}R_{20})_{n'}NHS(O)_2R_{25}$, $(CR_{10}R_{20})_{n'}C(Z)R_{13}$, or $(CR_{10}R_{20})_{n'}C(=NOR_{21})R_{13}$;

n' is an integer having a value of 1 to 10;

n is 0 or an integer from 1 to 10;

m is 0, or the integer 1 or 2;

R_3 is or $Q\text{-}(Y_1)_t$;

Q is an aryl or heteroaryl group;

t is a number having a value of 1, 2 or 3;

Z is oxygen or sulfur;

Y_1 is independently selected from hydrogen, C_{1-5} alkyl, halo-substituted C_{1-5} alkyl, halogen, or $-(CR_{10}R_{20})_nY_2$;

Y_2 is $-OR_8$, $-NO_2$, $-S(O)_{m'}R_{11}$, $-SR_8$, $-S(O)_{m'}OR_8$, $-S(O)_mNR_8R_9$, $-NR_8R_9$, $-O(CR_{10}R_{20})_nNR_8R_9$, $-C(O)R_8$, $-CO_2R_8$, $-CO_2(CR_{10}R_{20})_{n'}CONR_8R_9$, $-ZC(O)R_8$, -CN, $-C(Z)NR_8R_9$, $-NR_{10}C(Z)R_8$, $-C(Z)NR_8OR_9$, $-NR_{10}C(Z)NR_8R_9$, $-NR_{10}S(O)_mR_{11}$, $-N(OR_{21})C(Z)NR_8R_9$, $-N(OR_{21})C(Z)R_8$, $-C(=NOR_{21})R_8$, $-NR_{10}C(=NR_{15})SR_{11}$, $-NR_{10}C(=NR_{15})NR_8R_9$, $-NR_{10}C(=CR_{14}R_{24})SR_{11}$, $-NR_{10}C(=CR_{14}R_{24})NR_8R_9$, $-NR_{10}C(O)C(O)NR_8R_9$, $-NR_{10}C(O)C(O)OR_{10}$, $-C(=NR_{13})NR_8R_9$, $-C(=NOR_{13})NR_8R_9$, $-C(=NR_{13})ZR_{11}$, $-OC(Z)NR_8R_9$, $-NR_{10}S(O)_mCF_3$, $-NR_{10}C(Z)OR_{10}$, 5-(R_{18})-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

m' is a number having a value of 1 or 2;

R_4 is phenyl, naphth-1-yl or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substitiuent, is halo, cyano, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{23}$, $-(CR_{10}R_{20})_{m'''}COR_{36}$, SR_5, $-SOR_5$, $-OR_{36}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{36}$, $-NR_{10}C(Z)R_{23}$, or $-(CR_{10}R_{20})_{m'''}NR_{10}R_{20}$ and which, for other positions of substitution, is halo, cyano, $-C(Z)NR_{16}R_{26}$, $-C(Z)OR_8$, $-(CR_{10}R_{20})_{m'}COR_8$, $-S(O)_mR_8$, $-OR_8$, halo-substituted-C_{1-4} alkyl, $-C_{1-4}$ alkyl, $-(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_8$, $-NR_{10}S(O)_{m'}R_{11}$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_8$ or $-(CR_{10}R_{20})_{m'}NR_{16}R_{26}$; wherein m'' is 0 to 5 and m''' is 0 or 1;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moeities $-SR_5$ being $-SNR_7R_{17}$ and $-SOR_5$ being -SOH;

R_6 is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-5} cycloalkyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{22};

R_8 is hydrogen, heterocyclyl, heterocyclylalkyl or R_{11};

R_9 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R_8 and R_9 may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R_{12} is hydrogen, $-C(Z)R_{13}$ or optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted arylC_{1-4} alkyl, or $S(O)_2R_{25}$;

R_{13} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclylC_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl;

R_{14} and R_{24} is each independently selected from hydrogen, alkyl, nitro or cyano;

R_{15} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

R_{16} and R_{26} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to

7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12};

R_{18} and R_{19} is each independently selected from hydrogen, C_{1-4} alkyl, substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or together denote a oxygen or sulfur;

R_{21} is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl ;

R_{22} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{23} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-5} cycloalkyl;

R_{36} is hydrogen or R_{23};

R_{25} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

R_{27} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl, or aryl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein R_1 is optionally substituted 4-pyridyl, or 4-pyrimidinyl group.

3. The compound according to Claim 2 wherein the optional substituent is selected from alkyl, amino, or mono- or di-alkyl amino.

4. The compound according to Claim 3 wherein R_2 is an optionally substituted heterocyclic or heterocyclic alkyl moiety.

5. The compound according to Claim 2 wherein R_2 is morpholino, pyrrolidinyl, piperidinyl group, piperidinylalkyl, pyrrolidinylalkyl, morpholinoalkyl, and phenoxyalkyl, all of which may be optionally substituted; ethoxyalkyl, aminoalkyl, diethylamino, (phenylmethyl-N-methyl)aminoalkyl, or (phenylmethyl)amino-1-propyl.

6. The compound according to Claim 5 wherein R_2 is 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine.

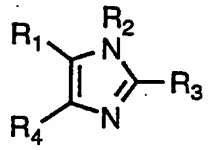
7. The compound according to Claim 1 wherein R_3, the group Q comprises an optionally substitued phenyl or thienyl moiety.

8. The compound according to Claim 7 wherein the substituent Q is phenyl substitued by halogen, halosubstituted alkyl, or -$(CR_{10}R_{20})_nY_2$ and Y_2 is -OR_8, -$S(O)_mR_{11}$, -SR_8, -$S(O)_mNR_8R_9$, or -NR_8R_9.

9. The compound according to Claim 1 wherein R_4 is optionally substitued phenyl, naphth-1-yl or naphth-2-yl wherein the 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl moiety are substituted by one or two substituents each independently selected from halogen, -SR_5, -SOR_5, -OR_{36}, or -$(CR_{10}R_{20})_mNR_{10}R_{20}$, and for other positions of substitution on these rings the substitution is halogen, -$S(O)_mR_8$, -OR_8, -$(CR_{10}R_{20})_mNR_{16}R_{26}$, -$NR_{10}C(Z)R_8$ and -$NR_{10}S(O)_mR_{11}$.

10. A pharmaceutical composition comprising a compound according to any of Claims 1 to 9 and a pharmaceutically acceptable carrier or diluent.

11. A compound of formula (I):



(I)

wherein:

R_1 is an optionally substituted 4-pyridyl or pyrimidinyl;

R_2 is hydrogen, C_{1-10} alkyl, heterocyclic alkyl, methyl S(O)m C_{1-4} alkyl;

R_3 is a 2- or 3-thiophene, or a substituted phenyl wherein the substituents are selected from methyl thio, methylsulfinyl, methylsulfonyl, methoxy, N-morpholinomethyl or -$C(=NOH)NH_2$;

R_4 is phenyl, naphth-1-yl, or naphth-2-yl which is optionally substituted by one or two substituents, each of which is independently selected halogen ,-SR_5, -SOR_5, -OR_{36}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, or -$(CR_{10}R_{20})_mNR_{10}R_{20}$ wherein m is 1 or 2,

R_5 is hydrogen, C_{1-4} alkyl, or NR_7R_{17}, excluding the moeities -SR_5 being -SNR_7R_{17} and -SOR_5 being -SOH;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{10};

R_{10} is hydrogen or C_{1-4} alkyl;

R_{36} is hydrogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-5} cycloalkyl; or a pharmaceutically acceptable salt thereof.

12. The compound of formula (I), according to Claim 11, which is:
4-[4-(4-Fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;
4-(1-Napthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(1-Napthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Napthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(2-Napthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-thiophene)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;
4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole;
or pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition comprising a compound according to Claim 11 or 12 and a pharmaceutically acceptable carrier or diluent.

14. A compound of formula (I), as defined in any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in therapy.

15. The use of a compound of formula (I), as defined in any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cytokine mediated disease state.

16. A method of treating a cytokine mediated disease in a mammal which comprises administering to a mammal in need of such treatment an effective cytokine-interferring amount of a compound of formula (I) according to any of claims 1 to 12 or a pharmaceutically acceptable salt thereof.

17. The method according to claim 16 wherein the mammal is afflicted with a cytokine mediated disease selected from rheumatoid arthritis, rheumatoid spondylitis,

osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, Crohn's disease, ulcerative colitis or pyresis.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 401/04; A61K 31/44
US CL : 546/278; 514/341
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/278; 514/341

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A, 3,929,807(FITZI) 30 DECEMBER 1975, COL.1,LINES 20-25, COL.18,LINES 25-28.	1-3,5,7-17
X	US,A, 3,772,441(LOMBARDINO ET AL.) 13 NOVEMBER 1973, COLUMN 2,LINES 5-10,COLUMN 12,LINES 4-5, COLUMN 13,LINES 20-25.	1-3,5,7-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 NOVEMBER 1994	21 NOV 1994

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	JANE FAN
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Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08297

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claim(s)1-13, drawn to compounds and compositions wherein R1 is pyridyl containg no hetero-substitutent and no additioal hetero moiety in any of other R's.

Group II, claim(s)1-13 , drawn to compounds and compositions wherein R1 is pyrimidyl, no additional hetero moiety in any of other R's.

Group III, claim(s) 1-13, drawn to compounds and compositions wherein R1 is quinolinyl, no additional hetero moiety in any of other R's.

Group IV, claim(s)1-13, drawn to compounds and compositions wherein R1 is pyridyl, other R's contain additional hetero-moiety. Each hetero-moiety or any combination thereof represents distinct inventions.

Group V, claim(s)1-13 , drawn to compounds and compositions wherein R1 is pyrimidyl, other R's contain hetero-moiety. Each hetero-moiety or any combination thereof represents distinct inventions.

Group IV, claims 1-13, drawn to compounds and compositions wherein R1 is quinolyl, other R's contain additional hetero-moiety.

Each hetero-moiety and any combination thereof represents distinct inventions. A first method of using in claims 14-17 will be considered along with any of the above group above elected.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Each time R's changes or any combinations thereof changes ,a different core is produced. Since no common core exist, the invention has no special technical feature.